Examiner admits that one skilled in the art would recognize that a gene product, such as a messenger RNA or protein, which is prevalent and highly specific to a disease, is "extremely useful as a marker for the detection of disease in that tissue". The Examiner also states that "[O]n the other hand, a gene product, i.e. either messenger RNA or protein which is prevalent and highly specific to one tissue type could be useful for the detection of that tissue type in metastatic lesions." However, the Examiner states that "no data is provided to teach the specificity of the detection of the claimed ESTs in clinical samples as indicative of colon disease or colon metastatic disease." The Examiner points to page 63, lines 25-33 of the specification where it states that a CS141 probe were found in 1.4 Kb mRNA in 1 of 6 normal colon samples and 4 of 6 cancerous colon samples. The Examiner points to Figures 4B and 5 as providing evidence that prostate tissue expressed CS141 as both mRNA and polypeptide. According to the Examiner, this does not constitute "persuasive evidence" that the ESTs corresponding to the consensus sequence of CS141 are colon specific or colon cancer specific. Therefore, according to the Examiner, the specification fails to demonstrate a specific correlation between the detection of the claimed ESTs and the presence of colon cancer or any other disease. Applicants respectfully traverse this rejection.

As discussed in Example 1 on pages 55-56, EST's corresponding to the consensus sequence of CS141 were found in 41.4% (24 of 58) of GI tract tissues. EST's corresponding to the consensus sequence of CS141 were found in 3.4 (17 of 506) of the other, non-GI tract tissues. Therefore, the consensus sequence or fragment thereof was found more than **12** times more often in GI tract than non-GI tract tissues.

As the Examiner correctly noted, on page 63 of the specification and in Figure 3A, the CS141 probe detected an approximately 1.4 kB RNA in a colon sample (lane 4) but not in any of the other eleven non-colon RNA samples (lanes 1, 2, 3 and 5-12). As shown in Figure 3B, the CS141 probe detected an approximately 1.4 Kb RNA in 1 of 6 normal colon specimens and in 4 of 6 colon cancer specimens. This data confirms the

tissue data discussed above in Example 1. As the data in Figures 3A and 3B show, CS141 is colon specific and is expressed in 5/12 or about 42% of colon tissues.

Fig. 4A shows that CS141 was present in 1 of 2 normal colon tissue samples (Lanes 2 and 5) and in 3 of 3 colon cancer tissue samples (Lanes 3, 4 and 6). Fig. 4B shows that CS141 was detected in colon cancer tissue (lane 4) and in one of two BPH prostate tissues (lane 8). CS141 was not detected using human placental DNA (lane 2) or in RNA isolated from tissues of normal colon (lane 3), breast (lanes 5-7), lung (lanes 11-13) or prostate cancer (lane 9).

As the data above clearly indicates, CS141 is a very tissue specific marker. Out of all the tissues looked at, only one BPH sample showed some expression of the marker. This is consistent with the data shown in Example 1 (discussed above) in which 3.4% of other tissues were found to express the marker. No marker is 100% expressed in one tissue type. As discussed in Applicants last two Amendments and Responses, the detection of CS141 outside of its normal host tissue, the gastrointestinal tract, is diagnostically useful as it serves as an indicator that the host (gastrointestinal tract) is in a diseased state. The identification of markers that are able to identify disease in this way is extremely valuable. Several different categories of markers are known that can be used to identify disease. One such category of markers are those that are genes that are expressed in a tissue-specific manner and at times appear in an inappropriate body compartment (See, specification, page 3, lines 16-29). The expression of a marker in a tissue or body compartment where their normal occurrence is very low or non-existent indicates that a disease has altered the marker so that it has escaped from its host tissue. Examples of markers that fall into this category are prostate specific antigen (PSA) and carcinoembryonic antigen (CEA). PSA is normally secreted at high levels into the seminal fluid and is present in very low levels in the blood of men with normal prostates. However, in patients with diseases of the prostate, including benign prostatic hyperplasia (BPH) or adenocarcinoma of the prostate, the level of PSA is markedly elevated in the blood and is a strong indication of disease of the prostate.

Similarly, CEA is a normal component of the inner lining of the colon and is present stool and in blood at low levels in people without disease of the colon. However, in disease of the colon, including inflammatory bowel disease and adenocarcinoma of the colon, the concentration of CEA is markedly elevated in the blood plasma or serum of many patients and is an indicator of disease of that tissue (such as colorectal cancer).

Additionally, like CS141, PSA and CEA are expressed in a few tissues other than the prostate and colon. Nonetheless, these markers are still recognized as useful in the diagnosis of disease of their primary tissue of origin due to their strong tissue selectivity.

Moreover, as discussed in the Declaration of Dr. Paula Friedman (Declaration) submitted in the Amendment and Response mailed on October 11, 2000, CS141 is characteristic of a tissue specific marker and able to act as a cancer diagnostic. According to the Declaration, CS141 is "clearly a GI specific marker, and therefore, its use as a GI tract cancer marker is unquestionable." Therefore, to one of ordinary skill in the art, the presence of CS141 outside of the gastrointestinal tract would indicate cancer development of that tissue, just as the presence of CEA and PSA outside of their respective tissues indicates cancer of the colon and prostate, respectively.

35 U.S.C. Section 101 has two purposes. First, 35 U.S.C. Section 101 defines the categories of inventions that are eligible for patent protection. An invention that is not a machine, an article of manufacture, a composition or a process cannot be patented. Second, 35 U.S.C. Section 101 serves to ensure that patents are granted on only those inventions that are "useful". *Manual of Patent Examining Procedure* Section 2107.01 (8th Edition, August 2001). Therefore, to satisfy the requirements of 35 U.S.C. Section 101, an applicant must claim an invention that is statutory subject matter and must show that the claimed invention is "useful" for some purpose, either explicitly or implicitly. *Id.*

To be "useful" for some purpose, the invention must have a specific and substantial utility (i.e. "a practical utility"). A "specific" utility is specific to the subject matter claimed (versus a "general utility" that would be applicable to a broad class of invention). A "substantial utility" defines a "real world" use. Not only must the invention have a specific and substantial utility, but this utility must be credible. Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g. test data, affidavits or declarations from experts in the art, patents or printed publications). *Manual of Patent Examining Procedure* Section 2107 (8th Edition, August 2001). An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. *Id.*

To properly reject a claimed invention under 35 U.S.C. Section 101, the Examiner must (a) make a *prima facie* showing that the claimed invention lacks utility, and (b) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (*Manual of Patent Examining Procedure* Section 2107.02 (8th Edition, August 2001)). The Examiner must do more than question the operability of the invention. Specifically, the Examiner must set forth factual reasons that would lead one skilled in the art to question the objective truth of the statement of operability. *Id.*

In view of the above arguments and the Declaration, Applicants respectfully submit that the Examiner has failed to make a *prima facie* showing that the claimed invention lacks utility. However, even assuming *arguendo* that the Examiner has made a *prima facie* showing that the claimed invention lacks utility, the Examiner has failed to provide a sufficient evidentiary basis for her factual assumptions relied upon in making this showing. Specifically, the Examiner has not provided any evidence refuting or contracting the statements supporting utility made in the Declaration of Dr. Friedman. Clearly, Dr. Friedman is one of ordinary skill in this art.

Therefore, Applicants submit that the rejection of claims 44-58 35 U.S.C. Section 101 is improper and should be withdrawn.

Rejection of Claims 44-58 Under 35 U.S.C. Section 112, First Paragraph

Claims 44-58 are rejected under 35 U.S.C. Section 112, first paragraph. The Examiner argues that since the claimed invention is not supported by a specific, substantial and credible utility, that one skilled in the art would not know how to use the claimed invention. Applicants respectfully traverse this rejection.

Applicants herein incorporate by reference their arguments made above in connection with the 35 U.S.C. Section 101 rejection. Therefore, in view of said arguments, Applicants submit that this rejection is improper and should be withdrawn.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 01-0025.

Respectfully submitted,
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